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Clinical Investigation

CLINICAL INVESTIGATION

Gradual withdrawal of remifentanil infusion may prevent opioid-induced hyperalgesia

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Abstract

Background: The aim of this study was to examine if gradual withdrawal of remifentanil infusion prevented opioid-induced hyperalgesia (OIH) as opposed to abrupt withdrawal. OIH duration was also evaluated.

Methods: Nineteen volunteers were enrolled in this randomized, double-blinded, placebo-controlled, crossover study. All went through three sessions: abrupt or gradual withdrawal of remifentanil infusion and placebo. Remifentanil was administered at 2.5 ng ml^{-1} for 30 min before abrupt withdrawal or gradual withdrawal by 0.6 ng ml^{-1} every five min. Pain was assessed at baseline, during infusion, 45–50 min and 105–110 min after end of infusions using the heat pain test (HPT) and the cold pressor test (CPT).

Results: The HPT 45 min after infusion indicated OIH development in the abrupt withdrawal session with higher pain scores compared with the gradual withdrawal and placebo sessions (both $P<0.01$. Marginal mean scores: placebo 2.90; abrupt 3.39; gradual 2.88), but no OIH after gradual withdrawal compared with placebo ($P=0.93$). In the CPT 50 min after end of infusion there was OIH in both remifentanil sessions compared with placebo (gradual $P=0.01$, abrupt $P<0.01$. Marginal mean scores: placebo 4.56; abrupt 5.25; gradual 5.04). There were no differences between the three sessions 105–110 min after infusion.

Conclusions: We found no development of OIH after gradual withdrawal of remifentanil infusion in the HPT. After abrupt withdrawal OIH was present in the HPT. In the CPT there was OIH after both gradual and abrupt withdrawal of infusion. The duration of OIH was less than 105 min for both pain modalities.

Clinical trial registration: NCT 01702389. EudraCT number 2011-002734-39.

Key words: analgesia, postoperative; analgesics, opioid; hyperalgesia; pain, postoperative; remifentanil

Opioids are paramount in the treatment of moderate and severe, acute pain and essential in general anaesthesia. The paradox that opioids may increase pain perception and the need for analgesics after end of administration has been studied in the last decades.[1–4] The phenomenon is termed opioid-induced hyperalgesia (OIH).[4–7] OIH is well documented in rodents,[8 9] and in experimental studies done with healthy volunteers.[10–12] It has been difficult to demonstrate OIH in clinical trials as a result of

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Editor's key points

- Opioid induced hyperalgesia (OIH) has been shown to occur in the perioperative period.
- Improved understanding is needed of OIH in the clinical setting, to minimize harm.
- The effect of variable reduction in remifentanil is studied on sensory responses in volunteers.
- Rapid withdrawal of remifentanil resulted in higher pain scores to heat than gradual withdrawal.
- Further study is needed to direct prevention and management of OIH.

the lack of good models, which eliminate both the problem of OIH masking by slowly eliminated analgesics necessary for postoperative pain relief, and the problem of differentiating between OIH and acute opioid tolerance. However, there are studies showing increased opioid consumption, higher pain scores and larger areas of pinprick hyperalgesia and allodynia near the wound after high-dose opioid infusion in patients.[1–3 13] The duration of OIH is also debated and varies between the opioids. Fentanyl has led to hyperalgesia for up to ten days post-injection in rodents,[8 9] while a meta-analysis on the clinical significance of OIH in surgical patients concluded that increased postoperative pain is present for up to 24 h after high-dose remifentanil infusion.[14]

There are many studies on OIH modulation with different adjuvants such as ketamine,[3 10] clonidine,[15] NSAID,[12] nitrous oxide,[16] propranolol[11] and propofol.[13] However, adjuvants have the disadvantage of possible unwanted effects. A different approach to prevent OIH, such as modulating the administration of the opioid, is therefore of interest. A study on spinal dorsal horns from rats showed that abrupt withdrawal of remifentanil induced long-term potentiation (LTP) in synapses, whereas a gradual withdrawal did not induce LTP.[17] This is of relevance because opioid withdrawal LTP shares pharmacology and signal transduction pathways with OIH.[17] The effect of gradual withdrawal of remifentanil infusion on hyperalgesia has not been studied in humans.[18] The main aim of our study was to evaluate the effect of gradual vs abrupt remifentanil withdrawal on OIH in humans. As a secondary aim we wanted to evaluate the duration of OIH after short-term and low-dose remifentanil infusion.

Methods

The protocol of this randomized, double-blinded, placebo-controlled, crossover study was approved by the Regional Committee for Medical Research Ethics in South Eastern Norway and The Norwegian Medicines Agency, and conducted in adherence to the guidelines for Good Clinical Practice.[19] The study was registered in www.clinicaltrials.gov (accessed 14 January 2016) (ID: NCT 01702389) and EudraCT (ref: 2011:002734:39).

We obtained written informed consent from the 19 subjects upon inclusion. The subjects were recruited through posters at the University of Oslo and Oslo University Hospital. Exclusion criteria were use of pain medication and complementary medicine, previous substance abuse, chronic illness, participation in other clinical trials the previous six months, and known allergies or serious side-effects to opioids. The subjects were informed not to drink alcohol 24 h before the sessions. Women were not included in the study because of variations in pain sensitivity during menstrual cycle that potentially could confound our findings.[20]

The subjects were familiarized with the numeric rating scale (NRS) for rating pain from 0 to 10 (0 = no pain, 10 = worst pain imaginable), the heat pain test (HPT)[21] and the cold pressor test (CPT)[22] before the first session. Each subject went through three sessions: abrupt withdrawal of remifentanil infusion (session A), gradual withdrawal of remifentanil infusion (session B) and placebo infusion with saline (NaCl 0.9%) (session C). There was a minimum interval of four days between each session. Computer-generated codes stored in sequentially numbered envelopes secured randomization of the sessions. A nurse anaesthetist not participating in the handling or evaluation of the subjects prepared remifentanil and saline in 50 ml syringes for infusion according to the randomization, thus blinding the investigators and the subjects.

Figure 1 illustrates the experimental setup. In all three sessions two infusion pumps (Orchestra® Base Primea, Fresenius Vial, 38590 Brezins, France) were running simultaneously to ensure the blinding. Infusion time and remifentanil dose were chosen based on a previous study done by our research group, demonstrating OIH after 30 min infusion of remifentanil with a target dose of 2.5 ng ml^{-1}.[12] In session A, pump 1 administered remifentanil until it was stopped abruptly after 30 min, while

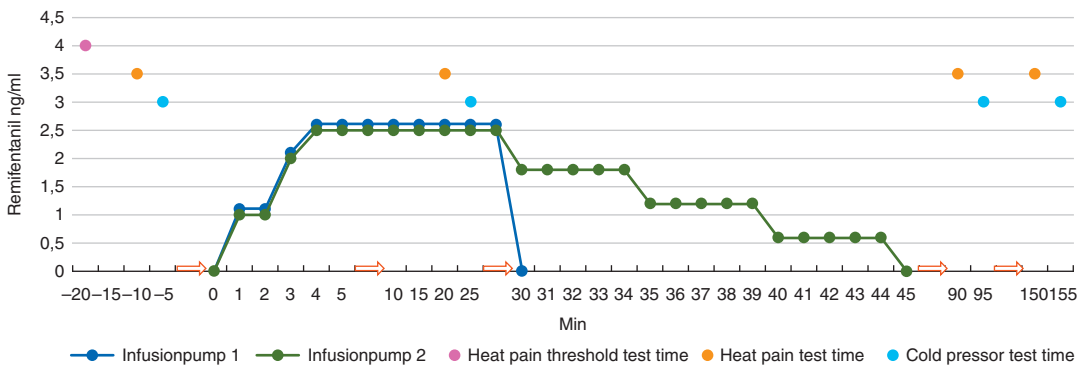

Fig 1 Schematic illustration of the experimental model. A heat pain threshold test was done 20 min before infusions at each session. Baseline pain for cold pressor test (CPT) and heat pain test (HPT) were scored with the numerical rating scale (NRS) 5–10 min before infusions. Pain assessment with HPT and CPT was done 20–25 min into infusion, 45–50 min after end of infusions and 105–110 min after end of infusions. Infusion pump 1 (abrupt withdrawal protocol) and 2 (gradual withdrawal protocol) were started simultaneously. The periods with gradual increase of remifentanil at start of infusion and the gradual withdrawal period have been accentuated with 1 min intervals.